Primary prevention aimed at avoiding or drastically reducing exposures will be the most efficient way to prevent environmentally associated cancers.

Evolution of Cancer Etiology and Primary Prevention

Primary prevention, broadly defined as the protection of health by personal and community-wide efforts (*1*), consists of measures aimed at preventing the inception of a pathologic process or the occurrence of a disease, in contrast with secondary prevention that consists of measures for the early detection and prompt intervention on a clinically asymptomatic disease. Referring to cancer, primary prevention mainly involves the avoidance or drastic reduction of exposure to carcinogenic risk factors.

Primary prevention of cancer has evolved through the ages, in close relation to the evolution in our understanding and interpretation of cancer etiology. In ancient times etiology and prevention of cancer were entirely included within the concept of this feared disease being equivalent to divine punishment. Recognition of one's sins, repentance, and pious obedient behavior opened the only available path to God's forgiveness and provided the only possible protection from cancer. Traces of such belief are still with us, not only as remainders of old superstitions but also as components of today's attribution of a prominent role in the origin of disease to individual behaviors, habits, and lifestyles. Individual behavior and lifestyle certainly play important roles, but today's trend appears to be that individuals are considered not only responsible for but also guilty of causing their disease, a situation very close to suffering the curse of God.

The spectrum of diseases considered to be self-inflicted is wide, ranging from those related to the use of tobacco to excessive alcohol consumption and from overnutrition to lack of exercise. However, the assumption that all behavioral choices are free choices does not reflect the actual situation. Apart from the obvious fact that certain individuals may be genetically predisposed to some conditions, the commonly used term "lifestyle" does not distinguish the various causes of habitual behavior, such as smoking, alcohol drinking, unhealthy dietary habits, and lack of physical exercise. Among these causes, social pressures and ubiquitous advertising play an essential role (*2*). Only a minority of inner-directed, strong-willed people can oppose or resist such pressures and make fully autonomous choices. Moreover individuals cannot really choose the socioeconomic situation in which to be born or their genetic background, and most workers cannot choose to avoid working in hazardous industries or occupations.

The only time that cancer was considered to be transmissible was between the seventeenth and eighteenth centuries. Special hospitals were built in certain European countries to isolate patients with cancer, almost in the same way as was done for patients with leprosy (*3*). Relatively soon, however, the conviction that cancer was not contagious prevailed again. It was strengthened during the glorious period of microbiology by the inability to identify a germ or bacterium that could be related to cancer. This may perhaps partly explain the scant attention paid to the experiments of Peyton Rous (*4*) at the beginning of the twentieth century on the role of viruses in the origin of tumors.
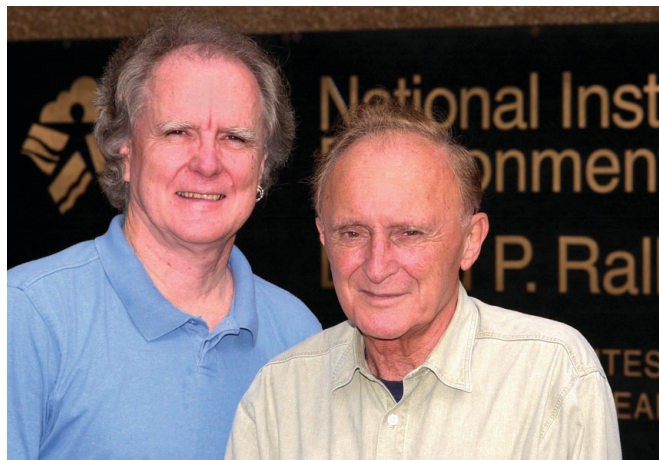
James Huff and Lorenzo Tomatis

In the first half of the twentieth century, the hypothesis of a viral origin for human cancer gained the support of great scientists such as Oberling in France and Zilber in the former Soviet Union (*5*). It became a favorite hypothesis at the time of President Nixon's war against cancer in the early 1970s, and has recently returned to the stage with renewed strength (*6*).

Besides the hypothesis of infectious (parasitic or viral) etiology, other early prevailing speculations on the origins of cancer have been the cell irritation theory, proposed by Virchow, and the embryonic "cell rest" theory of Conheim, who proposed that tumors arise from embryonic cells that fail to mature and persist in the tissues (*3,7–9*). Of more than anecdotal interest may be that the 1905 report of the Huntington Cancer Research Fund, noting the unsuccessful attempts made to identify the causes of cancer, stated that "It has therefore seemed advisable … to branch out into new methods, and attempt to investigate, not so much the cause of cancer as the conditions under which it may arise" with the "hope that by collecting a number of data a deeper insight into the question may ultimately be obtained, and a nearer approach be made to a conception of the nature of the processes involved" (*8*). In spite of the obviously different levels of knowledge and the magnitude of progress, the predominant trend in cancer research today could be described in not too dissimilar words.

For many decades there was a strong rivalry between proponents of chemical carcinogenesis and of viral carcinogenesis that was based partly on different schools of thought, but this rivalry was also largely related to competition for research funds. Scientists in the field of viral carcinogenesis, and later of molecular biology, were generally of the opinion that those involved in chemical carcinogenesis were old-fashioned and perhaps also not particularly brilliant (*10–12*), while those working in chemical carcinogenesis looked with skepticism at viral oncologists. In terms of funding and popularity, chemical carcinogenesis prevailed until the late 1960s and early 1970s. Then came Nixon's declaration of war against cancer that led to the belief that the dread disease could be conquered with the same kind of concerted effort that split the atom and landed humans on the moon. The search for a viral etiology of human cancer was launched as a glorious challenge, and viral carcinogenesis, in particular the studies on the viral origin of human leukemia, obtained considerable increases in funding.

The causes of cancer have been divided roughly into two broad categories: exogenous (or environmental) and endogenous (or genetic), a division that has been operationally useful because it favored the concentration and funding of efforts that, on the basis of technology and methods available at the time, offered the greatest possibility of success. For a long time, this meant that the prevailing area of cancer research focused on the identification of exogenous environmental, and for a long time mainly occupational, causes of human cancer. Expansion of research on environmental and occupational causes of cancer also coincided with, and possibly contributed to, growing awareness of the relationships between socioeconomic conditions and health, and to a tendency toward decreasing the inequalities in health care and services. However, not much progress has been made toward actually reaching a greater social and health equity worldwide (13,14).

The first environmental agents to be identified as human carcinogens were tobacco snuff (15), a life habit related to habitual consumption, and chimney soot (16), which is related to occupational exposures. A century later, they were followed by arsenic used in therapy (17), aromatic amines (18), and thereafter by a long series of chemicals or chemical mixtures that, for the most part, were found to be human carcinogens in the working environment (19). All of these agents were identified on the basis of clinical observations, case reports, or epidemiologic studies. Most of these carcinogens were actually identified in situations that, to a considerable extent, mimicked experimental conditions of long-term carcinogenicity bioassays: relatively small population groups exposed to high concentrations of hazardous agents in a closed environment. The carcinogens identified in the working environment were called occupational carcinogens, a term that was often interpreted to imply that their carcinogenicity was not only directly related but also limited to the occupational setting. However, agents that were identified as human carcinogens within the working environment (e.g., benzene, asbestos) do not cease to be carcinogenic when encountered at lower concentrations in the general environment, often for long periods.

Ionizing radiation is another prominent environmental agent identified as being carcinogenic at the beginning of the twentieth century. Ionizing radiation was discovered by Roentgen in 1895 (20) and introduced into medical practice soon thereafter. It took only 7 years for scientists to determine and report that ionizing radiation induced tumors in exposed individuals (21,22). This was a particularly short delay, compared with the much longer periods required for the recognition of chemicals introduced into the environment as human carcinogens. However, in spite of the rapidity with which the awareness of radiation carcinogenicity was acquired, it was 40 more years before it became accepted that natural radioactivity present in uranium mines was also carcinogenic (23). Further, several decades elapsed before it became officially recognized that radioactivity in the general environment at much lower concentrations also represented a carcinogenic risk (24). Ionizing radiation thus provides a pertinent example of how long the stepwise process can last beginning with the scientific observation of the carcinogenicity of an environmental agent to the official recognition of a cancer risk to humans at both high and low levels of exposure.

As a matter of fact, in spite of the convincing evidence of their carcinogenicity, the adoption of measures to avoid exposure to even the most obvious carcinogenic hazards has encountered continued and serious obstacles and unjustified delays. Aromatic amines were shown to be carcinogenic in exposed workers at the end of the nineteenth century (18) and the International Labour Office officially declared benzidine and 2-naphthylamine as human carcinogens in 1921 (25), but the first official action toward phasing out these aromatic amines was not taken until the late 1960s. The first report of an increased risk for lung cancer in workers exposed to bischloromethylether is dated 1962, but no action was taken, under various pretexts, until 1975 (26). Many other examples pertain as well. More recently, in 1985 the National Toxicology Program (NTP) showed that 1,3-butadiene was a potent carcinogen at 6.5 ppm and most likely below that level of exposure, and yet the occupational exposure standard was not lowered until November 1996 (27,28).

Legislation prohibiting the manufacture of a limited number of chemicals identified as human carcinogens was introduced in the late 1960s in several industrialized countries, but did not cover the same chemical carcinogens in each country. In addition, the criteria to determine which chemicals may be hazardous to humans on the basis of the experimental evidence of carcinogenicity varied considerably from country to country and were, in general, overly exclusive (29,30). Nevertheless, due to the combined effect of banning or reducing exposure to certain carcinogens, the modernization of many industrial production processes, the overall reduction of the number of industrial workers, and the transfer of hazardous industries to developing countries, the number of occupational cancers has decreased in most industrialized countries. However, occupational cancers are now becoming a very serious problem in developing countries where industrialization is a rather recent phenomenon and where exposure levels to hazardous chemicals considerably exceed regulatory levels established in industrialized countries (31,32).

Because most human carcinogens that have been identified within the first half of the twentieth century were occupational carcinogens, prevention of human cancer became focused on eliminating, or reducing to a minimum, occupational exposures to identified human carcinogens. During that same period results from long-term animal bioassays provided evidence for the carcinogenicity of additional chemicals, and attempts were made to deal with these carcinogenic agents as if they were de facto human carcinogens (19,33,34). The International Agency for Research on Cancer (35) recommended that

> "in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans."

Likewise, the NTP considers chemicals shown to be carcinogenic in animals without any human evidence as being "reasonably anticipated to be carcinogenic to humans" (36).

The credibility of experimental results as effective predictors of human risk was systematically questioned by industry. The industry point of view was supported by numerous scientists, either because they had working or financial relations with industry or because, in good faith, they asked for a degree of certainty greater than the available methods could actually provide. In parallel, regulatory agencies and health authorities often pretended a full assurance that findings of experimental studies were truly predictive of similar outcomes in humans, whereas doubtful or inadequate negative epidemiologic observations were sometimes inappropriately considered as more relevant than positive experimental results (37). As a consequence, in spite of the fact that sufficient information was available for its implementation on a wide scale, primary prevention has continued to encounter serious obstacles and unjustifiable delays.

Research on the endogenous component of the carcinogenesis process gained importance and gradually took over when methods of molecular biology began to be applied to cancer research. Cancer virology, which received a generous share of the funds made available by the Nixon administration, did not produce the hoped-for solution to the cancer riddle, but it did contribute to the development of scientists with new skills. These scientists became essential to the rapid development of molecular biology and molecular genetics and thus played an important role in the shift of scientific interest.

This was probably one of the most significant (albeit unintended) results from the war on cancer. Even the strongest traditional

disciplines, such as biochemistry and pathology and more recently epidemiology, are now becoming "molecular." In parallel with the growing role of research on the endogenous and genetic causes of cancer and, above all, on the mechanisms underlying the carcinogenesis processes, interest in the role of socioeconomic factors and public health as a whole has decreased (13). Genetics is, however, also the study of how memories of the past are preserved in our genes and of the way such memories sway interactions with the present and future. This is perhaps one of the few good auspices for the future in a period that seems to be dominated by attempts to suppress history and memories.

For many decades primary prevention of cancer was implemented on the basis of evidence for a causal relationship between an exposure and human cancer that took into consideration biological plausibility, but was independent from any degree of understanding of underlying mechanisms. One of the credos of public health has been that prevention can be implemented before having established causality or before reaching a complete understanding of mechanisms. The rapid development and expansion of molecular biology and molecular genetics has provided methods and tools that permit investigations of some of the finer details of the carcinogenesis processes. A deeper knowledge of mechanisms may allow future interventions aimed at stopping the sequence of events leading to tumor development, invasiveness, and metastases and may substantially improve therapeutic interventions. However, at present, the emphasis on research into the pathogenesis of cancer seems to have encouraged an almost complete, hopefully temporary, elimination of reliance and research on etiology and prevention.

From a period in which cancer causes, or components of causes, were identified with little understanding of the underlying mechanisms, we have entered a period in which the understanding of mechanisms progresses rapidly without as yet contributing to the identification of new carcinogenic agents or the definition of primary prevention strategies. In this context, a most urgent and complicated issue is development of a better understanding of the role of low-level exposures to multiple risk factors and of the extent and nature of their possible interaction. The most reasonable and socially acceptable development of prevention should be the blending of the population approach (i.e., a shifting of the distribution of risk factors across an entire population in a favorable direction) with the high-risk approach (i.e., the intervention on individuals predisposed to the disease) (38). Interventions aimed at reducing or eliminating genetically determined weaknesses in the interaction with the environment will, therefore, not in any way make obsolete or redundant interventions aimed at eliminating or reducing exposures to environmental carcinogens and at improving socioeconomic conditions (39). Exposure to environmental carcinogens causes cancer, and it is therefore obvious that measures of primary prevention aimed at avoiding or drastically reducing exposures will be the most efficient way to prevent environmentally associated cancers. In addition, primary prevention by protecting the health of all individuals has an intrinsic characteristic of universality that diagnostic and therapeutic approaches do not have because they may unavoidably introduce a potential for discrimination on socioeconomic grounds. Furthermore, suggested priorities centered on primary prevention are clearly in keeping with the precautionary principle (40).

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